PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	143.70	143.91

FILE 'CAPLUS' ENTERED AT 15:50:02 ON 12 DEC 2002
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FILE COVERS 1907 - 12 Dec 2002 VOL 137 ISS 24
FILE LAST UPDATED: 11 Dec 2002 (20021211/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s l3
L4 9 L3

=> d bib abs hitstr 1-9

L4 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2002 ACS
AN 2002:575064 CAPLUS
DN 137:125091
TI Preparation of 2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-diones, related compounds, and compositions thereof as TNF-.alpha. inhibitors for treatment of cancer, inflammatory disorders, heart disease, and related disorders
IN Robarge, Michael J.; Chen, Roger Shen-Chu; Muller, George W.; Man, Hon-Wah
PA Celgene Corporation, USA
SO PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002059106	A1	20020801	WO 2001-US50401	20011221

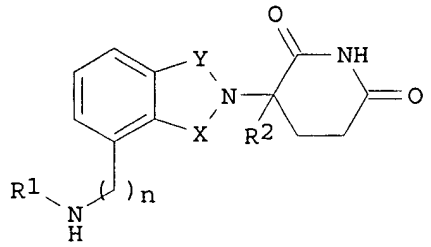
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

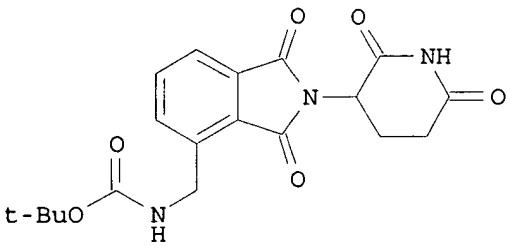
PRAI US 2000-258372P P 20001227
US 2001-972487 A 20011005

OS MARPAT 137:125091

GI



I



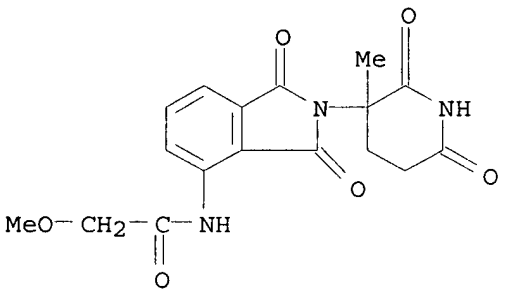
II

AB Title isoindole-imides I [wherein one of X and Y is CO and the other is CH2 or CO; R1 = H, (cyclo)alkyl, alkenyl, alkynyl, benzyl, aryl, alkylheterocycloalkyl, alkylheteroaryl, COR3, CSR3, CO2R4, alkyl-(NR6)2, alkyl-OR5, alkyl-CO2R5, CONHR3, CSNHR3, CON(R3)2, CSN(R3)2, or alkyl-OCOR5; R2 = H, benzyl, alkyl, alkenyl, or alkynyl; R3 = independently (cyclo)alkyl, alkenyl, alkynyl, benzyl, aryl, alkylheterocycloalkyl, alkylheteroaryl, alkyl-N(R6)2, alkyl-OR5, alkyl-CO2R5, alkyl-OCOR5, or CO2R5; R4 = alkyl, alkenyl, alkynyl, alkyl-OR5, benzyl, aryl, alkylheterocycloalkyl, or alkylheteroaryl; R5 = alkyl, alkenyl, alkynyl, benzyl, aryl, or heteroaryl; R6 = independently H, alkyl, alkenyl, alkynyl, benzyl, (hetero)aryl, or alkyl-CO2R5; or R6 groups may join to form a heterocycloalkyl group; n = 0-1; with the proviso that when n = 0, R1 .noteq. H; or pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, or mixts. of stereoisomers thereof] were prepd. for reducing the level of cytokines and their precursors in mammals. In particular, the invention pertains to isoindole-imide compds. that are potent inhibitors of the prodn. of TNF-.alpha. (no data). For example, Me 2-(methoxycarbonyl)-3-nitrobenzoate was hydrogenated with 10% Pd/C (87%). The amine was converted to the nitrile by diazonium salt formation effected by treatment with NaNO3 followed by cyanide formation using classic Sandmeyer procedure (65%). The nitrile was reduced with 10% Pd/C in MeOH and aq. HCl under hydrogen to afford Me 3-aminomethyl-2-(methoxycarbonyl)benzoate.bul.HCl (90%), which was treated with TEA and then reacted with di-t-Bu dicarbonate to give the carbamate (93%). Cyclization with 3-aminoglutarimide.bul.HCl using diisopropylethylamine in DMF produced II (82%). The 2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-diones and pharmaceutical compns. comprising them are useful for treating or preventing diseases or disorders in mammals, e.g. cancers, such as

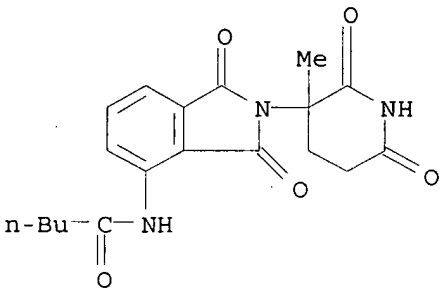
solid tumors and blood-born tumors; heart disease, such as congestive heart failure; osteoporosis; and genetic, inflammatory, allergic, and autoimmune diseases (no data).

IT **444288-45-3P**, 2-Methoxy-N-[2-(3-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide **444288-47-5P**, Pentanoic acid [2-(3-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amide **444288-49-7P**, Heptanoic acid [2-(3-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amide **444288-51-1P**, 3-Chloro-N-[2-(3-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]benzamide **444288-53-3P**, N-[2-(3-Methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]propionamide **444288-55-5P**, Thiophene-2-carboxylic acid [2-(3-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]amide **444288-88-4P** **444288-99-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(TNF-.alpha. inhibitor; prepn. of (oxopiperidyl)isoindolinone TNF-.alpha. inhibitors by cycloaddn. of aminoglutarimides to carboxybenzoates)

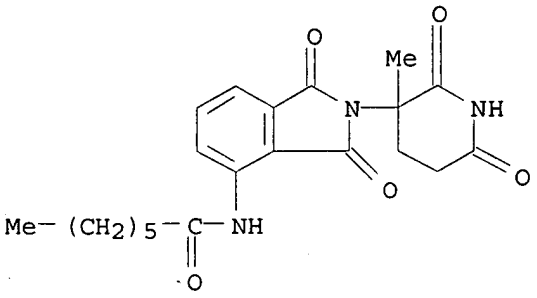
RN 444288-45-3 CAPLUS
CN Acetamide, N-[2,3-dihydro-2-(3-methyl-2,6-dioxo-3-piperidinyl)-1,3-dioxo-1H-isoindol-4-yl]-2-methoxy- (9CI) (CA INDEX NAME)



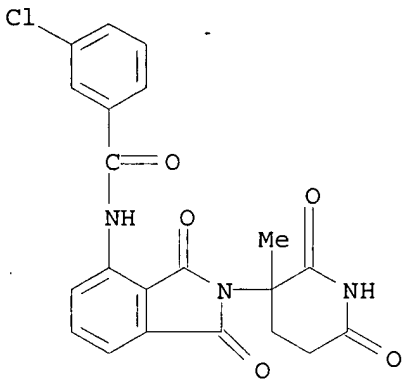
RN 444288-47-5 CAPLUS
CN Pentanamide, N-[2,3-dihydro-2-(3-methyl-2,6-dioxo-3-piperidinyl)-1,3-dioxo-1H-isoindol-4-yl]- (9CI) (CA INDEX NAME)



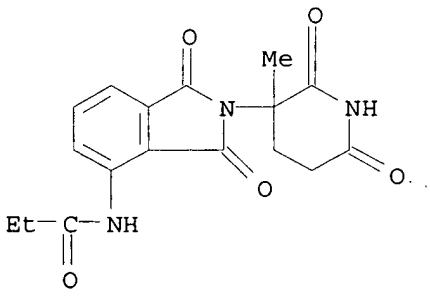
RN 444288-49-7 CAPLUS
CN Heptanamide, N-[2,3-dihydro-2-(3-methyl-2,6-dioxo-3-piperidinyl)-1,3-dioxo-1H-isoindol-4-yl]- (9CI) (CA INDEX NAME)



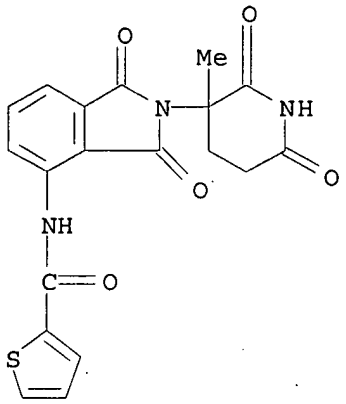
RN 444288-51-1 CAPLUS
CN Benzamide, 3-chloro-N-[2,3-dihydro-2-(3-methyl-2,6-dioxo-3-piperidinyl)-1,3-dioxo-1H-isoindol-4-yl]- (9CI) (CA INDEX NAME)



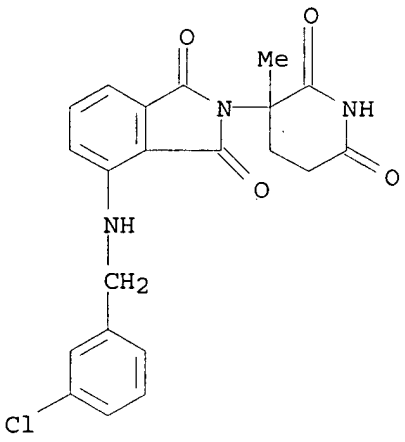
RN 444288-53-3 CAPLUS
CN Propanamide, N-[2,3-dihydro-2-(3-methyl-2,6-dioxo-3-piperidinyl)-1,3-dioxo-1H-isoindol-4-yl]- (9CI) (CA INDEX NAME)



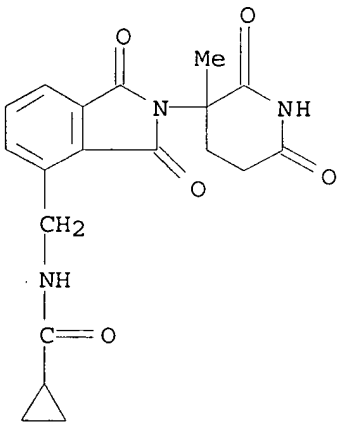
RN 444288-55-5 CAPLUS
CN 2-Thiophenecarboxamide, N-[2,3-dihydro-2-(3-methyl-2,6-dioxo-3-piperidinyl)-1,3-dioxo-1H-isoindol-4-yl]- (9CI) (CA INDEX NAME)



RN 444288-88-4 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-[[(3-chlorophenyl)methyl]amino]-2-(3-methyl-2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



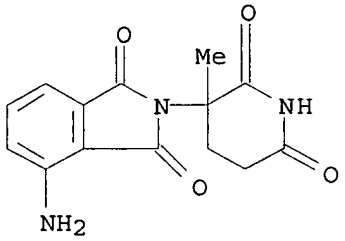
RN 444288-99-7 CAPLUS
CN Cyclopropanecarboxamide, N-[[2,3-dihydro-2-(3-methyl-2,6-dioxo-3-piperidinyl)-1,3-dioxo-1H-isoindol-4-yl]methyl]- (9CI) (CA INDEX NAME)



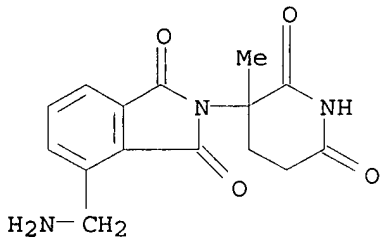
IT **202271-87-2**, 4-Amino-2-(3-methyl-2,6-dioxopiperidin-3-yl)isoindole-1,3-dione **444289-00-3**, 4-(Aminomethyl)-2-(3-methyl-2,6-dioxo-3-piperidyl)isoindoline-1,3-dione monohydrochloride

RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; prepn. of (oxopiperidyl)isoindolinone TNF-.alpha. inhibitors by cycloaddn. of aminoglutarimides to carboxybenzoates)

RN 202271-87-2 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(3-methyl-2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 444289-00-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-(aminomethyl)-2-(3-methyl-2,6-dioxo-3-piperidinyl)-, monohydrochloride (9CI) (CA INDEX NAME)



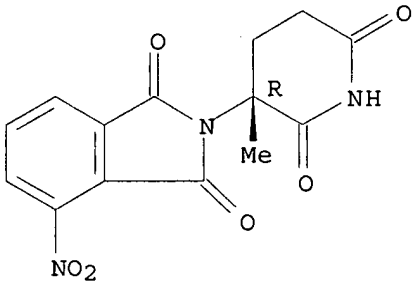
● HCl

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2002 ACS
AN 2002:211227 CAPLUS
DN 137:241664
TI Thalidomide and its analogues as cyclooxygenase inhibitors
AU Noguchi, Tomomi; Shimazawa, Rumiko; Nagasawa, Kazuo; Hashimoto, Yuichi
CS Institute of Molecular & Cellular Biosciences, The University of Tokyo, Bunkyo-ku, Tokyo, 113-0032, Japan
SO Bioorganic & Medicinal Chemistry Letters (2002), 12(7), 1043-1046
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
AB Thalidomide showed cyclooxygenase (COX)-1/2 inhibitory activity with a potency comparable to that of aspirin. Structural development studies of thalidomide resulted in potent COX-1/2 inhibitors, and COX-1-selective and COX-2-selective inhibitors.
IT **212394-02-0 212394-04-2 212394-08-6**
212394-10-0
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide and analogs as cyclooxygenase inhibitors)

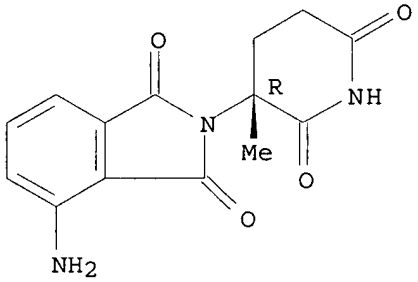
RN 212394-02-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]-4-nitro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



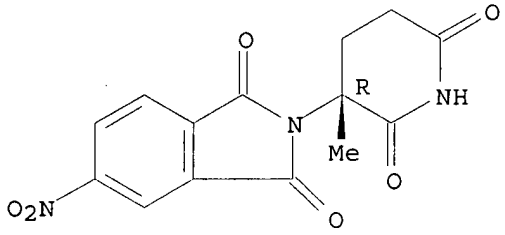
RN 212394-04-2 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



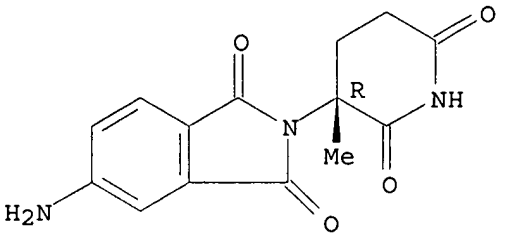
RN 212394-08-6 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]-5-nitro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 212394-10-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

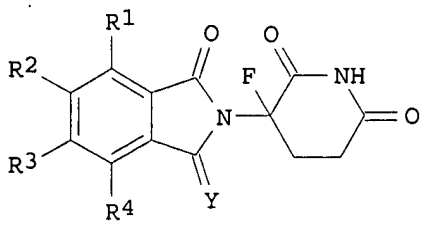


RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2002 ACS
AN 1999:603139 CAPLUS
DN 131:214197
TI Preparation of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines for reducing inflammatory cytokine levels.
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu; Man, Hon-wah
PA Celgene Corp., USA
SO U.S., 12 pp., Cont. -in-part of U. S. 5,874,448.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5955476	A	19990921	US 1998-42274	19980313
	US 5874448	A	19990223	US 1997-976140	19971118
	CA 2317834	AA	19990916	CA 1998-2317834	19981117
	WO 9946258	A1	19990916	WO 1998-US24453	19981117
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9914138	A1	19990927	AU 1999-14138	19981117
	AU 752958	B2	20021003		
	EP 1062214	A1	20001227	EP 1998-958016	19981117
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002506068	T2	20020226	JP 2000-535637	19981117
	BR 9815613	A	20020528	BR 1998-15613	19981117
	NO 2000002529	A	20000630	NO 2000-2529	20000516
	FI 2000001192	A	20000714	FI 2000-1192	20000518
PRAI	US 1997-976140	A2	19971118		
	US 1998-42274	A	19980313		
	WO 1998-US24453	W	19981117		

OS MARPAT 131:214197
GI



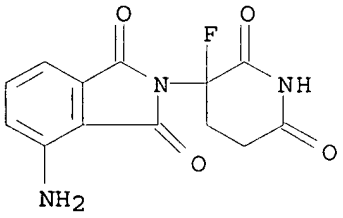
I

AB Title compds. (I; Y = O, H2; R1-R4 = H, halo, alkyl, alkoxy, amino), were prepd. for redn. of tumor necrosis factor and interleukin levels (no data). Thus, a soln. of 1,3-dioxo-2-(1-tert-butoxycarbonyl-2,6-dioxopiperidin-3-yl)isoindoline (prepn. given) in THF at -40.degree. was treated with Li[N(SiMe3)]2 soln. and then with N-fluorobenzenesulfonimide followed by stirring overnight to give 10% 1,3-dioxo-2-(1-tert-butoxycarbonyl-2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline. The latter was stirred with HCl in dioxane for 3 days to give 77% 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline. Drug formulations contg. the latter are given.

IT **220460-56-0 220460-57-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines for reducing inflammatory cytokine levels)

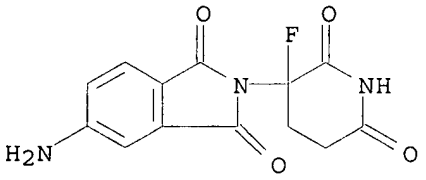
RN 220460-56-0 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)



RN 220460-57-1 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)



RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2002 ACS

AN 1999:595162 CAPLUS

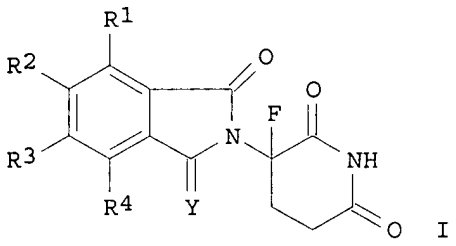
DN 131:228653

TI Preparation of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and their use to reduce tumor necrosis factor .alpha. levels

IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu; Man, Hon-wah
PA Celgene Corporation, USA
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9946258	A1	19990916	WO 1998-US24453	19981117
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 5955476	A	19990921	US 1998-42274	19980313
	CA 2317834	AA	19990916	CA 1998-2317834	19981117
	AU 9914138	A1	19990927	AU 1999-14138	19981117
	AU 752958	B2	20021003		
	EP 1062214	A1	20001227	EP 1998-958016	19981117
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002506068	T2	20020226	JP 2000-535637	19981117
	BR 9815613	A	20020528	BR 1998-15613	19981117
	NO 2000002529	A	20000630	NO 2000-2529	20000516
	FI 2000001192	A	20000714	FI 2000-1192	20000518
PRAI	US 1998-42274	A	19980313		
	US 1997-976140	A2	19971118		
	WO 1998-US24453	W	19981117		

OS MARPAT 131:228653
GI



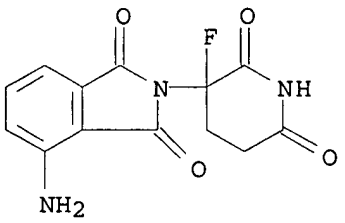
I

AB 1-Oxo- and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines (I; R1-R4 = H, halo, C1-4 alkyl, C1-4 alkoxy, amino; Y = O, H2) and their acid addn. salts reduce the levels of inflammatory cytokines, e.g., TNF-.alpha. in mammals (no data). A typical embodiment is 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline which was prepd. by N-protection of 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)isoindoline with (Me3CO2C)2O (90%), fluorination of N-BOC-protected intermediate with (PhSO2)2NF in presence of BuLi or (Me3Si)2NLi (10%), and deprotection with HCl (dioxane soln.) (77% yield). Tablets, capsules and injection or infusion solns. contg. I are formulated.

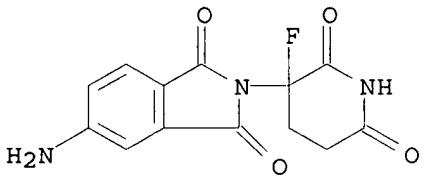
IT **220460-56-0P 220460-57-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and their use to reduce tumor necrosis factor .alpha. levels)

RN 220460-56-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)

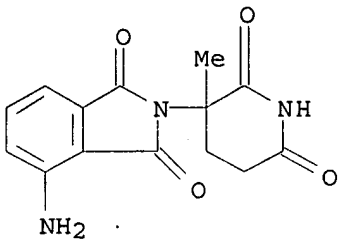


RN 220460-57-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2002 ACS
AN 1999:386135 CAPLUS
DN 131:129881
TI Amino-substituted thalidomide analogs: potent inhibitors of TNF-.alpha. production
AU Muller, George W.; Chen, Roger; Huang, Shaei-Yun; Corral, Laura G.; Wong, Lu Min; Patterson, Rebecca T.; Chen, Yuxi; Kaplan, Gilla; Stirling, David I.
CS Celgene Corporation, Warren, NJ, 07059, USA
SO Bioorganic & Medicinal Chemistry Letters (1999), 9(11), 1625-1630
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
AB Thalidomide is a known inhibitor of TNF-.alpha. release in LPS stimulated human PBMC. Herein we describe the TNF-.alpha. inhibitory activity of amino substituted analogs of thalidomide and its isoindolin-1-one analog, EM-12. The 4-amino substituted analogs were found to be potent inhibitors of TNF-.alpha. release in LPS stimulated human PBMC.
IT **202271-87-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(amino derivs. of thalidomide and EM-12 as inhibitors of TNF-.alpha. prodn.)
RN 202271-87-2 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(3-methyl-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)

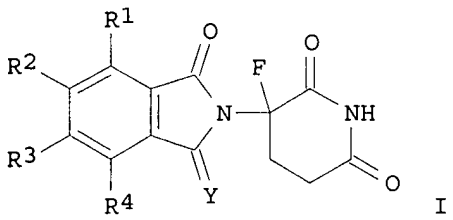


RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2002 ACS
AN 1999:136769 CAPLUS
DN 130:168244
TI Substituted 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and method of reducing TNF.alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-Chu; Man, Hon-Wah
PA Celgene Corporation, USA
SO U.S., 10 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5874448	A	19990223	US 1997-976140	19971118
	US 5955476	A	19990921	US 1998-42274	19980313
	NO 2000002529	A	20000630	NO 2000-2529	20000516
	FI 2000001192	A	20000714	FI 2000-1192	20000518
PRAI	US 1997-976140	A2	19971118		
	US 1998-42274	A	19980313		
	WO 1998-US24453	W	19981117		

OS MARPAT 130:168244
GI



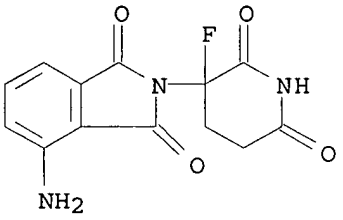
I

AB 1-Oxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines reduce the levels of TNF.alpha. in mammals (no data), and may be useful in the treatment of viral infections. The compds. I [Y = O or H2; R1, R2, R3, and R4 = H, halo, C1-4 alkyl or alkoxy, or amino], and their acid addn. salts when a protonatable N atom is present, are claimed. A typical embodiment is 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline (II), i.e. I [Y = O, R1-R4 = H]. This compd. was prepd. in a variety of ways. For instance, the non-fluorinated analog of II was N-BOC-protected on its piperidine ring, lithiated with BuLi in THF, fluorinated with N-fluorobenzenesulfonimide, and deprotected with HCl, to give II.

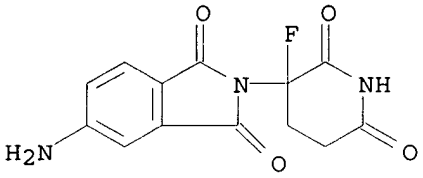
IT **220460-56-0P**, 1,3-Dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)-4-

aminoisoindoline **220460-57-1P**, 1,3-Dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)-5-aminoisoindoline **220460-76-4P**, 1,3-Dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)-5-aminoisoindoline hydrochloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compd.; prepn. of substituted (dioxofluoropiperidinyl)isoindolines and method of reducing TNF.alpha. levels)

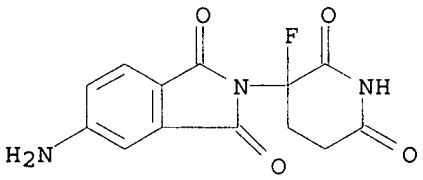
RN 220460-56-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)



RN 220460-57-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)



RN 220460-76-4 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

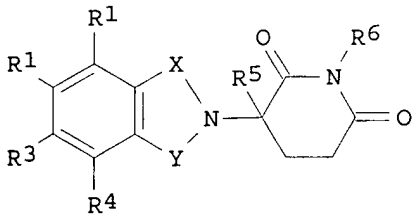
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2002 ACS
AN 1998:795004 CAPLUS
DN 130:38290
TI Substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and 1-oxoisoindolines and method of reducing tnf.alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu

PA Celgene Corporation, USA
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9854170	A1	19981203	WO 1998-US10886	19980528
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9877012	A1	19981230	AU 1998-77012	19980528
	AU 741982	B2	20011213		
	EP 984955	A1	20000315	EP 1998-924959	19980528
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002501536	T2	20020115	JP 1999-500909	19980528
	FI 9902490	A	20000127	FI 1999-2490	19991123
	NO 9905751	A	20000128	NO 1999-5751	19991123
	US 6395754	B1	20020528	US 2000-445002	20000222
	US 2002173658	A1	20021121	US 2002-143416	20020510
PRAI	US 1997-48278P	P	19970530		
	WO 1998-US10886	W	19980528		
	US 2000-445002	A1	20000222		

OS MARPAT 130:38290
GI



I

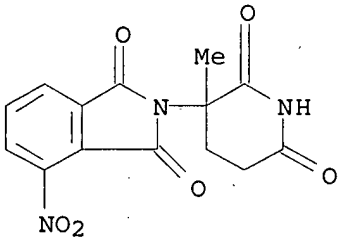
AB Substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and 1-oxo-2-(2,6-dioxopiperidin-3-yl)isoindolines (I) (one of X and Y = CO and the other is CH2 or CO; R1, R2, R3, R4 independently is halo, C1-4-alkyl or -alkoxy or one of R1, R2, R3, R4 is (un)substituted NH2 and the others are H; R5 = H or C1-8-alkyl, benzo, Cl, F; R6 = substituted CH2O(CO)R8CH2NH2 (R8 = m- or p-phenylene of (CH2)n (n = 1-4))) were claimed to reduce the levels of TNF.alpha. in a mammal. I (R6 = H) were prepd. and used in pharmaceutical compns. Thus 1-oxo-2-(2,6-dioxo-3-methylpiperidin-3-yl)-4,5,6,7-tetrafluoroisoindoline was prepd. in a multistep reaction initially from methylglutamic acid which was converted via many steps to .alpha.-amino-.alpha.-methylglutarimide which was converted visa many steps to the final product.

IT **202271-74-7P 202271-87-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(for prepn. of dioxopiperidinylphthalimides and oxoisoindolines for

redn. of TNF.alpha. levels)

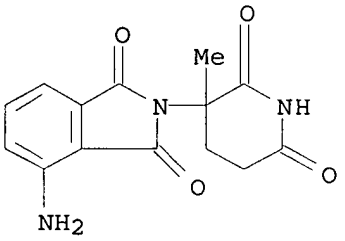
RN 202271-74-7 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(3-methyl-2,6-dioxo-3-piperidinyl)-4-nitro- (9CI) (CA INDEX NAME)



RN 202271-87-2 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(3-methyl-2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2002 ACS

AN 1998:486299 CAPLUS

DN 129:216494

TI Tumor necrosis factor-alpha production enhancing activity of substituted 3'-methylthalidomide: influence of substituents at the phthaloyl moiety on the activity and stereoselectivity

AU Miyachi, Hiroyuki; Kolso, Yukiko; Shirai, Ryuichi; Niwayama, Satomi; Liu, Jun O.; Hashimoto, Yuichi

CS Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, 113-0032, Japan

SO Chemical & Pharmaceutical Bulletin (1998), 46(7), 1165-1168
CODEN: CPBTAL; ISSN: 0009-2363

PB Pharmaceutical Society of Japan

DT Journal

LA English

OS CASREACT 129:216494

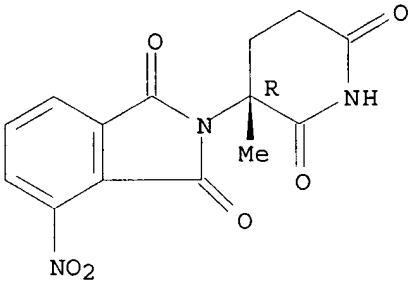
AB The synthesis and tumor necrosis factor (TNF)-.alpha. prodn. enhancing activity of substituted 3'-methyl-thalidomides on human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate (TPA) was described. Though the introduction of an electron-donating amino group at the phthaloyl moiety of .alpha.-methylthalidomides enhanced the activity, substituted .alpha.-methylthalidomides showed decreased stereoselectivity as compared to that of non-substituted .alpha.-methylthalidomide. The data indicates that the TNF-.alpha. prodn. enhancing activity of thalidomide derivs. depends on both the electronic-state of substituents at the fused benzene ring and the stereochem. of the glutarimide moiety. (S)-4-amino-3'-methylthalidomide induced a 695% increase in the amt. of

tumor necrosis factor-alpha prodn. at 0.3.mu.m by the human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate.

IT **212394-02-0P 212394-03-1P 212394-04-2P**
212394-05-3P 212394-08-6P 212394-09-7P
212394-10-0P 212394-11-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tumor necrosis factor-alpha prodn. enhancing activity of substituted 3'-methylthalidomides)

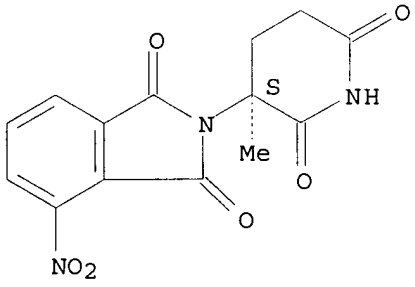
RN 212394-02-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]-4-nitro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



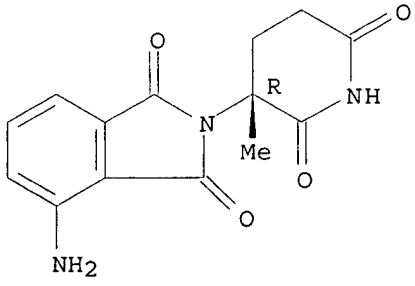
RN 212394-03-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[(3S)-3-methyl-2,6-dioxo-3-piperidinyl]-4-nitro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



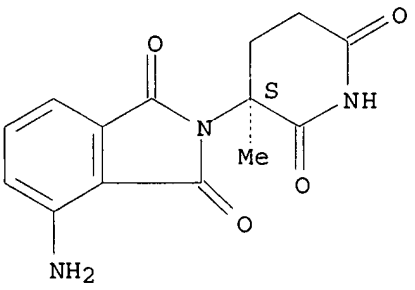
RN 212394-04-2 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



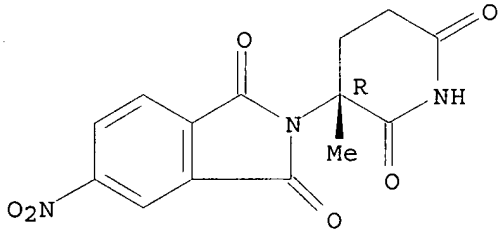
RN 212394-05-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3S)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



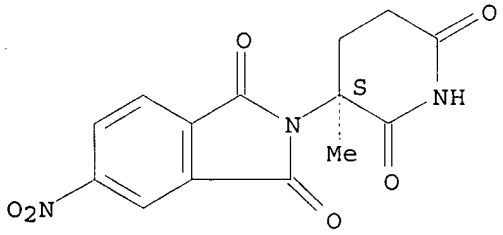
RN 212394-08-6 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]-5-nitro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



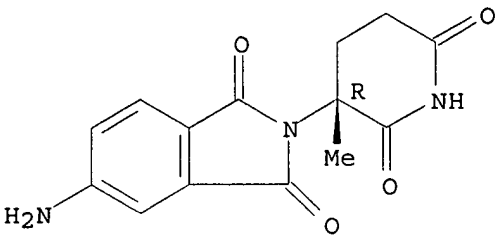
RN 212394-09-7 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-[(3S)-3-methyl-2,6-dioxo-3-piperidinyl]-5-nitro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



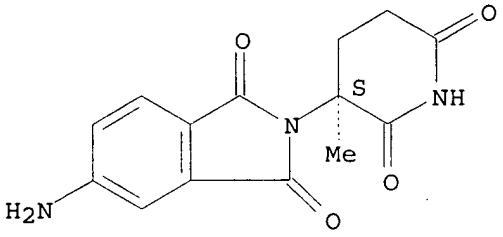
RN 212394-10-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 212394-11-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-[(3S)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2002 ACS
AN 1998:87727 CAPLUS
DN 128:140615
TI Substituted 2-(2,6-dioxo-3-piperidinyl)phthalimides and -1-oxoisoindolines and method of reducing TNF-.alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu
PA Celgene Corp., USA; Muller, George W.; Stirling, David I.; Chen, Roger Shen-Chu
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9803502	A1	19980129	WO 1997-US13375	19970724
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5635517	A	19970603	US 1996-690258	19960724
	US 5635517	B1	19990629		
	US 5798368	A	19980825	US 1996-701494	19960822
	AU 9738998	A1	19980210	AU 1997-38998	19970724
	AU 715779	B2	20000210		
	EP 925294	A1	19990630	EP 1997-936295	19970724
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2001503384	T2	20010313	JP 1998-507259	19970724
	RU 2177944	C2	20020110	RU 1999-103124	19970724

	FI 9900101	A	19990319	FI 1999-101	19990119
	US 6281230	B1	20010828	US 2000-543809	20000406
	US 6476052	B1	20021105	US 2000-633908	20000807
	US 6316471	B1	20011113	US 2000-634061	20001017
	US 6335349	B1	20020101	US 2000-716528	20001120
	US 2002045643	A1	20020418	US 2001-781179	20010212
	US 2002183360	A1	20021205	US 2002-119486	20020410
PRAI	US 1996-690258	A	19960724		
	US 1996-701494	A	19960822		
	WO 1994-US7411	A	19940701		
	US 1996-701499	A1	19960724		
	US 1997-48278P	P	19970530		
	WO 1997-US13375	W	19970724		
	US 1999-230389	B3	19990507		
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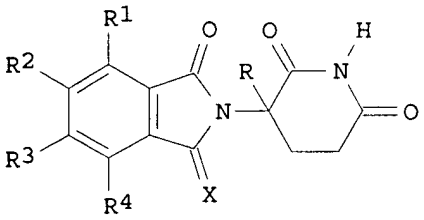


I

AB Title compds. I (X = O, H2; R = H, alkyl, benzyl, halo; R1, R2, R3, R4 = H, alkyl, alkoxy, halo, amino) were prepd. for TNF-.alpha. redn. in mammals. Thus, I (X = O, R = R1 = R3 = R4 = H, R2 = NO2), prepd. from 4-nitrophthalic anhydride and .alpha.-aminoglutarimide hydrochloride, was hydrogenated over 10% Pd/C in 1,4-dioxane at 50 psi for 6.5 h to give 69% I (X = O, R = R1 = R3 = R4 = H, R2 = NH2). Several examples of formulations were given.

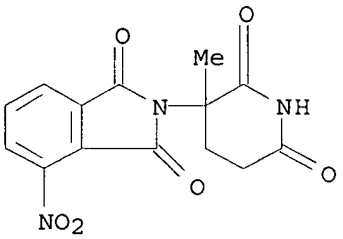
IT **202271-74-7P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(2-(2,6-dioxo-3-piperidinyl)phthalimides and -1-oxoisoindolines for reducing TNF-.alpha. levels)

RN 202271-74-7 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(3-methyl-2,6-dioxo-3-piperidinyl)-4-nitro- (9CI) (CA INDEX NAME)



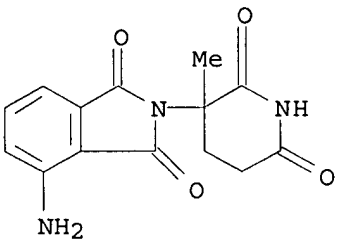
IT **202271-87-2P**

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(2-(2,6-dioxo-3-piperidinyl)phthalimides and -1-oxoisoindolines for reducing TNF-.alpha. levels)

RN 202271-87-2 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(3-methyl-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)



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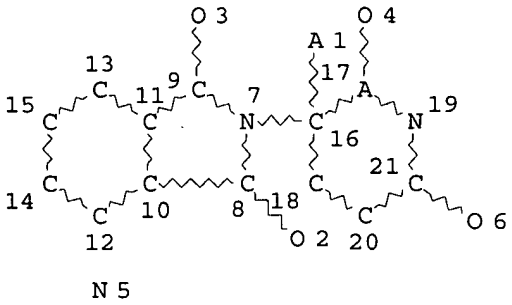

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SEARCH TIME: 00.00.01

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L3 22 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN Cyclopropanecarboxamide, N-[[2,3-dihydro-2-(3-methyl-2,6-dioxo-3-piperidinyl)-1,3-dioxo-1H-isoindol-4-yl]methyl]- (9CI)
MF C19 H19 N3 O5